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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/777,484	02/05/2001	John H. Griffin	SCRIP1200-1	8867

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/777,484	GRIFFIN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,9,10,12,13,15,16 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,9,10,12,13,15,16 and 19* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The finality of the Office action mailed 30 June 2003 is hereby withdrawn in view of the new grounds of rejection set forth below. See MPEP § 706.07(d).

Status of Application, Amendments and/or Claims

The amendment of 05 December 2003 has been entered in full. Claims 1, 4-5, 7, 9, 12-13, 15, 19 are amended. Claims 3, 6, 8, 11, 14, 17-18, and 20-21 are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2, 4-5, 7, 9-10, 12-13, 15-16, and 19 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The rejection to claims 1-16 and 19-21 under 35 U.S.C. § 112, first paragraph, as set forth at pg 2-10 of the previous Office Action (30 June 2003) is *withdrawn* in view of the amended and cancelled claims and Applicant's persuasive arguments (05 December 2003). Please see section on 35 U.S.C. § 102(b) and 102(e), below.

2. The rejections to claims 1-16 and 19-21 under 35 U.S.C. § 112, second paragraph, as set forth at pg 10-11 of the previous Office Action (30 June 2003) are *withdrawn* in view of the amended and cancelled claims (05 December 2003). Please see section on 35 U.S.C. § 112, second paragraph below.

Claim Rejections - 35 USC § 112

3. Claims 9, 12-13, 16, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 9, 12-13, 16, and 19 are indefinite because claim 9 does not have a step that clearly relates back to the preamble. For example, the preamble of claim 9 recites a method for reducing inflammation in a subject while the last step of the claim recites that APC reduces *neurological* inflammation in the subject. It is noted to Applicant that this issue could be overcome by amending the preamble of claim 9 to recite "A method for reducing *neurological* inflammation in a subject..."

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-2, 4, 9-10, 12, and 15 are rejected under 35 U.S.C. 102(e) as being anticipated by Grinnell et al. (U.S. Patent 6,268,337).

Grinnell '337 teaches the intravenous administration of activated protein C (APC) to subjects with vascular occlusive and arterial thromboembolytic disorders (col 3-4; col 8, lines 28-33). Grinnell '337 also discloses that the administration of APC is beneficial in preventing

the local extension of the microvascular and macrovascular occluding arterial thrombus, thereby reducing the neurological deficit resulting from the stroke (abstract). The claims of the instant application recite that subjects *at risk* of having a stroke may be administered APC. An entire population, such as humans, may be at risk of having a stroke and therefore it would be desirable to administer APC to each individual.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2, 4-5, 7, 9-10, 12-13, 15, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grinnell et al. (U.S. Patent 6,268,337) in view of Arnljots et al. (Arterio Thromb Vasc Biol 15: 937-941, 1995) and Hickenbottom et al. (Semin Neurol. 18(4):485-492, 1998).

Grinnell '337's teachings are disclosed above.

However, Grinnell '337 does not teach the administration of a therapeutically effective amount of protein S. Grinnell '337 also does not teach the administration of a NMDA receptor antagonist or a calcium ion channel antagonist. Arnljots et al. teaches that the anti-coagulant action of APC is enhanced by the nonenzymatic cofactor, Protein S (pg 937, ¶ 3). Arnljots teaches the coadministration of APC and Protein S to a rabbit model of microarterial thrombosis ("Results", pg 938-939). Arnljots et al. discloses that, in considering the use of APC as an antithrombotic agent in humans, their findings suggest coadministration of Protein S to be beneficial (pg 940, last ¶). Hickenbottom et al. teaches that NMDA receptor antagonists and calcium channel antagonists are neuroprotective agents that are administered to acute stroke patients (abstract; pg 487, col 2 through pg 489).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the APC administration method as taught by Grinnell '337 by coadministering Protein S and an NMDA receptor antagonist or a calcium ion channel antagonist as taught by Arnljots et al and Hickenbottom, respectively. The person of ordinary skill in the art would have been motivated to make that modification because blood coagulation is a complex process regulated by the balance of pro-coagulant and anticoagulant mechanisms, wherein this balance determines normal hemostasis or abnormal pathological thrombus formation. The person of ordinary skill in the art reasonably would have expected success because previous studies indicated the antithrombotic effects of APC, the powerful potentiation of APC's effect by Protein S, and the neuroprotective effect of NMDA antagonists and calcium

channel antagonists. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

It is noted to Applicant that the same patient population is treated with the same compound in the claimed invention of the instant application as that of Grinnell '337. Therefore, the same inherent results are produced. Also, the claims recite that subjects *at risk* of having a stroke may be administered APC. An entire population, such as humans, may be at risk of having a stroke and therefore it would be desirable to administer APC to each individual. A compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43). Simply stating a new property of APC does not render the method of protecting neuronal cells from cell death in a subject or reducing inflammation in a subject of the instant application free of the art. Furthermore, the claims of the instant application do not recite any specific dosages of APC.

10. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Grinnell et al. (U.S. Patent 6,268,337), Arnljots et al. and Hickenbottom as applied to claims 1-2, 4-5, 7, 9-10, 12-13, 15, and 19 above, and further in view of Grinnell et al. (U.S. Patent 6,071,514).

Grinnell et al. '337, Arnljots et al., and Hickenbottom do not teach the administration of a therapeutically effective amount of one or more anticoagulant, anti-platelet or thrombolytic agent.

Grinnell '514 teaches the intravenous administration of activated protein C (APC) to subjects with thrombotic disorders (including, but not limited to, stroke, venous thrombosis, myocardial infarction, unstable angina, etc.) (col 3, lines 34-67 through col 4). Grinnell '514

also discloses that APC may be administered alone or in combination with an antiplatelet agent thrombolytic agent (col 3, lines 34-52).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the APC administration method as taught by Grinnell '337 by coadministering Protein S, an NMDA receptor antagonist or a calcium ion channel antagonist, and/or an anti-platelet agent as taught by Arnljots et al, Hickenbottom, and Grinnell et al. '514, respectively. The person of ordinary skill in the art would have been motivated to make that modification because blood coagulation is a complex process regulated by the balance of pro-coagulant and anticoagulant mechanisms, wherein this balance determines normal hemostasis or abnormal pathological thrombus formation. The person of ordinary skill in the art reasonably would have expected success because previous studies indicated the antithrombotic effects of APC, the powerful potentiation of APC's effect by Protein S, the neuroprotective effect of NMDA antagonists and calcium channel antagonists, and the reduction of the tendency of platelets in the blood to clump and clot after administration of anti-platelet factors (like aspirin). Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

It is noted to Applicant that the same patient population is treated with the same compound in the claimed invention of the instant application as that of Grinnell '514. Therefore, the same inherent results are produced. Also, the claims recite that subjects *at risk* of having a stroke may be administered APC. An entire population, such as humans, may be at risk of having a stroke and therefore it would be desirable to administer APC to each individual. A compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43). Simply stating a new property of APC does not render the

method of protecting neuronal cells from cell death in a subject or reducing inflammation in a subject of the instant application free of the art. Furthermore, the claims of the instant application do not recite any specific dosages of APC.

11. Claims 15-16 and 19 are rejected under 35 U.S.C. 103(a) as being anticipated by Griffin et al. (U.S. Patent No. 5,084,274) in view of Arnljots et al. (Arterio Thromb Vasc Biol 15: 937-941, 1995).

Griffin et al. teaches the intravenous administration of activated protein C (APC) to subjects with arterial thrombotic occlusion or thromboembolism (col 3, lines 8-19; col 5-8). Griffin et al. also discloses that APC may be administered alone or in combination with a thrombolytic agent (col 2, lines 9-20). The state of the art is such that arterial thrombotic occlusion or thromboembolism are inflammatory vascular diseases characterized by the closure of a blood vessel by a blood clot causing blockage of blood flow. An inflamed arterial segment has the tendency to embolize tiny particles of microparticulate atheromatous debris, platelet thrombi, or both, into the microvasculature. Elevated levels of circulating inflammatory mediators in patients with ischemic heart disease have also been reported (see for example, Yamada et al. Am Heart J 140: S90-S102, 2000).

Griffin et al. does not teach the administration of a therapeutically effective amount of protein S.

Arnljots et al. teaches that the anti-coagulant action of APC is enhanced by the nonenzymatic cofactor, Protein S (pg 937, ¶ 3). Arnljots teaches the coadministration of APC and Protein S to a rabbit model of microarterial thrombosis ("Results", pg 938-939). Arnljots et

al. discloses that, in considering the use of APC as an antithrombotic agent in humans, their findings suggest coadministration of Protein S to be beneficial (pg 940, last ¶).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the APC administration method as taught by Griffin et al. by coadministering Protein S as taught by Arnljots et al. The person of ordinary skill in the art would have been motivated to make that modification because blood coagulation is a complex process regulated by the balance of pro-coagulant and anticoagulant mechanisms, wherein this balance determines normal hemostasis or abnormal pathological thrombus formation. The person of ordinary skill in the art reasonably would have expected success because previous studies indicated the antithrombotic effects of APC and the powerful potentiation of this effect by Protein S. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

It is noted to Applicant that the same patient population is treated with the same compound in the claimed invention of the instant application as that of Griffin et al. Therefore, the same inherent results are produced. Also, the claims recite that subjects *at risk* of having a stroke may be administered APC. An entire population, such as humans, may be at risk of having a stroke and therefore it would be desirable to administer APC to each individual. A compound and all of its properties are inseparable; they are one and the same thing (see *In re Papesch*, CCPA 137 USPQ 43). Simply stating a new property of APC does not render the method of reducing inflammation in a subject of the instant application free of the art. Furthermore, the claims of the instant application do not recite any specific dosages of APC.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

BEB
Art Unit 1647
22 April 2004

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER